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ASD TECHNICAL REPORT 61-744

THE RESPONSE OF ANIMALS INHALING HYDROGEN FLUORIDE FOR SINGLE, SHORT EXPOSURES

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MIPR No. (33-616) 60-32

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ASD TR 61-744	U.S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland THE RESPONSE OF ANIMALS INHALING HYDROGEN FLUORIDE FOR SINGLE, SHORT EXPOSURES, by T. R. Carson, et al. December 1961. 20p. incl. illus., tables. 6 refs. (Proj. 7165: Task 716501) Rats were exposed to various concentrations of HF for single 5-, 15-, 30-, and 60-minute periods, and the LC50's were calculated. Guinea pigs were exposed for 15 minutes to various concentrations and the LC50 calculated. In addition to the lethal exposures, rats, dogs, and rabbits were exposed to	ASD TR 61-744	lower concentration levels ranging from 6 to 50 percent of the rat LC50's. The toxic signs were eye and nasal irritation. There were gross changes in the lungs of all species exposed to HF at the higher concentrations. The signs and pathologic changes decreased in severity as the concentration levels were lowered. At a given concentration levels were lowered. At a given concentration level were lowered as and rabbits tolerated HF better than rats. The concentrations of HF causing mild toxic signs and no gross changes in the lungs of rats were 307 ppm (0.3 mg/liter) and 103 ppm (0.08 mg/liter) for 15 and 60 minutes, respectively.	
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THE RESPONSE OF ANIMALS INHALING HYDROGEN FLUORIDE FOR SINGLE, SHORT EXPOSURES

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FOREWORD

The investigations described herein were performed during the period from April to August 1961 by T. R. Carson, M. H. Weeks, F. T. Wilinski, and F. W. Oberst, of the U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland. The work was performed under MIPR (33-616) 60-32, Project No. 7165, "Health Hazards of Materials and Radiation", Task No. 716501, "Evaluation and Control of Toxic Chemical Materials". The contract monitor was Dr. Kenneth C. Back, Toxic Hazards Section, Biomedical Laboratory, Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio.

Two other reports of work performed under this MIPR have previously been prepared; they are: "The Response of Animals Inhaling Nitrogen Dioxide for Single, Short-Term Exposures", and "Vapor Toxicity of UDMH in Rats and Dogs from Short Exposures".

The experiments reported herein were conducted according to the "Rules Regarding Animal Care" established by the American Medical Association.

ABSTRACT

Rats were exposed to various concentrations of HF for single 5-, 15-, 30-, and 60-minute periods, and the LC50's were calculated. Guinea pigs were exposed for 15 minutes to various concentrations and the LC50 calculated. In addition to the lethal exposures, rats, dogs, and rabbits were exposed to lower concentration levels ranging from 6 to 50 percent of the rat LC50's. The toxic signs were eye and nasal irritation. There were gross changes in the lungs of all species exposed to HF at the higher concentrations. The signs and pathologic changes decreased in severity as the concentration levels were lowered. At a given concentration level dogs and rabbits tolerated HF better than rats. The concentrations of HF causing mild toxic signs and no gross changes in the lungs of rats were 307 ppm (0.3 mg/liter) and 103 ppm (0.08 mg/liter) for 15 and 60 minutes, respectively.

PUBLICATION REVIEW

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THE RESPONSE OF ANIMALS INHALING HYDROGEN FLUORIDE FOR SINGLE, SHORT EXPOSURES

INTRODUCTION

Hydrogen fluoride (HF) vapor probably will be one of the products found in the exhaust funcs of some of the advenced missiles. The possibility of men being exposed to high concentrations of this vapor for short periods of time has therefore become considerably greater. Exposure to HF vapor may also occur in industries manufacturing, using, or storing this acid gas. These increased exposure possibilities have created the need for additional toxicological information to aid in estimating safe concentrations of HF in single, short exposures of men.

Animal studies for single, short exposure periods by Machle et al. (2), showed that concentrations of 1835 ppm (1.5 mg/l) of HF and above were injurious to rabbits and guinea pigs regardless of exposure time. They also found that these animal species exposed to concentrations of 1223 ppm (1.0 mg/l) of HF and below for periods up to 30 minutes did not die but did show evidence of tissue damage. Their conclusion was that HF is primarily an eye and a respiratory irritant which in high concentrations produces pathologic changes in some visceral organs.

To aid in an estimate of safe limits of HF for short exposure periods in man, it was necessary first to expand on Machle's experiments by determining dose-mortality curves at short exposure times by using more species and larger numbers of animals at each exposure time. The toxic signs and gross pathologic effects of HF at progressively lowered concentrations for short exposures were determined to permit estimation of the concentrations causing minimal or no effects in animals.

EXPERIMENTAL PROCEDURES

A. Exposure Technique

1. Dispersion

The HF* vapor was metered from a cylinder, maintained at 88°C in an oil bath, into a stainless steel expansion tank. The vapor passed from the expansion tank through a manometer containing kerosene

^{*}Purchased from the Matheson Co., Inc., E. Rutherford, New Jersey.

into a glass mixing bowl and then into a 400 liter dynamic gassing chamber operated at an air flow of 200 liters per minute. The expansion tank and manometer were housed in a constant temperature box maintained at 68°C. The mixing bowl was coated with a layer of paraffin to minimize reaction of HF with the glass. The manometer, constructed of copper tubing (1/2 inch diameter), was a modification of the one described by Peterson (3). All the lines between the cylinder and the mixing bowl were of copper tubing, 1/4 inch diameter. The orifices used in the manometer were made of stainless steel discs with bores ranging from 0.004 to 0.052 inch.

2. Collection and Analysis of Chamber Air Samples

Chamber air samples were collected either in gas bottles varying in volume from 1000 to 3000 ml or in two absorbers in series, each containing 20 ml of 0.2 N NaON. The results from these two sampling techniques agreed very well as long as the sampling tube did not exceed 6 inches in length. Beyond this length the fall-out in the sampling tube caused the wet sample to contain about 60 percent of that in the gas bottle sample. The sampling rate was from 0.4 to 1 liter per minute. After collecting a sample in the gas bottle, the bottle was cooled in a dry-ice-acetone bath, after which the 0.2 N NaOH was introduced. The samples were brought to a constant volume with demineralized water, aliquots taken for analysis, and titrated by a modification of the method described by Willard and Winter (5). For the 5- and 15-minute exposures, samples were taken before and during exposure. For all other exposure times, two to three samples were taken during exposure. All concentrations are expressed as ppm and mg/liter of HF.

B. Exposure and Observation of Animals

1. LC50 Exposures

Young, white, male rats (100 to 120 gm) were exposed in groups of 10 to various concentrations of HF vapor for single 5-, 15-, 30-, and 60-minute periods. The LC50 for each exposure time was calculated by the method of Bliss (1). The survivors were weighed daily and observed for 14 days after exposure and were sacrificed at the end of this observation period.

Young, white, male guinea pigs (342 to 363 gm) were exposed in groups of 10 to various concentrations of HF vapor for a 15-minute period, and the LC50 was calculated. The survivors were weighed daily and observed for 14 days after exposure and were then killed for pathologic studies.

2. Sub Lethal Exposures

Since it was shown in the above LC50 exposure studies that toxic signs, body weight suppression, and gross pathologic changes occurred, preliminary tests were carried out to determine whether these measures might serve as sensitive criteria for effects of HF on animals exposed to sub lethal concentrations. Young male rats (100 to 120 gm) and young male guinea pigs (225 to 285 gm) were exposed in groups of 10 to HF at concentrations of 1377 ppm (1.13 mg/liter) for 30 minutes. This concentration was approximately 68 percent of the 30-minute LC50 for the rat. The body weight changes for both species and a similar non exposed group, serving as controls, were observed for 6 weeks.

Since Machle et al. (2) indicated that HF vapor produced pathology in certain visceral organs, we believe that weight changes in these organs might also be a useful criterion for measuring HF effects. This criterion was evaluated in a preliminary experiment on a group of 20 young male rats (100 to 120 gm) exposed for 15 minutes to HF at a concentration level of 1768 ppm (1.45 mg/liter). This concentration approximated 66 percent of the 15 minute LC50 value for the rat. The survivors were killed in groups of 4 at various intervals between 4 hours and 14 days after exposure. Spleen, kidneys, liver, and lungs were weighed from the animals.

Since no changes in body weights and in organ weights of these animals were found, only toxic signs and gross pathologic changes were used in subsequent experiments to evaluate the changes in HF effects with concentration. Rats, rabbits, guinea pigs, and mongrel dogs were exposed to various concentrations of HF below the LC50's for rats. The exposure concentration, in terms of percent of the LC50 (50, 25, 12.5, and 6 percent) for the rat, the time of HF exposure, and the animal species used are shown in table 1. Toxic signs were observed during the exposure and for as long as 45 days after exposure. Dogs were bled weekly for 2 to 3 weeks prior to exposure and 1 to 3 weeks after exposure for hematocrits, red, white and differential cell counts (6). One dog was sacrificed at 7 days and the other at 21 days after exposure for pathologic studies.

C. Pathology

Organs from animals surviving the LC50 exposure were examined for gross changes. The organs included lungs, liver, spleen, kidneys and heart. Organs from the animals exposed to the sub lethal levels were examined at various times between 4 hours and 45 days after exposure. Control animals were killed at times similar to those of the exposed.

TABLE 1

EXPOSURE SEQUENCES FOR VARIOUS SPECIES TO SUB LETHAL CONCENTRATIONS OF HF VAPOR

		No. Animals In Exposure	දු	nc. of Hi	. Approx	imating	the Perce	ntages of	the 1050	Gone. of HF Approximating the Percentages of the 1650's for Rats
Species	S	Group	503	2	25%	-0	12.53	53	69	
			mdd	mg/1	mdd	mg/1	mdd	mg/1	add	mg/1
Rats		&	2432	1.99	1,138	1.18	6ħL	c.61	not	not done
Rats		8	1410	1.15	290	8 ⁴ .0	376	0.31	307*	0.30
Rabbits	its	· S	1247	1.02	851	69.0	not	not done	not	not done
Dogs		αı	OL C	not done	989	水。	760	0.38	not	not done
Rats		10	1377	1.13	no	not done	not	not done	not	not done
Guin	Guinea Pigs	10	1377	1.13	no	not done	not	not done	not	not done
Rats	_	ଷ	684	O+1*0	291	0.24	126	0.10	103*	90.08
Dogs	ro.	α	ST.	not done	243	0.20	157	0.13	not	not done

* Groups of 15 animals were used.

RESULTS

A. Exposure and Observation of Animals

1. LC50 Exposures

The 5-, 15-, 30-, and 60-minute LC50 values for rats and 15-minute LC50 value for guinea pigs with 19/20 confidence limits and slopes of the dose-response curves with their standard errors are shown in table 2. Eye and nose irritation were present in both species, as shown by reddened conjunctiva, pawing at the nose, and marked eye and nasal secretion and sneezing. The eye and nasal irritation were not seen a week after exposure. Respiratory distress, body weight loss, general weakness for 2 to 3 days, and death also were seen. The surviving rats had a 10 to 15 percent loss in body weight compared to the controls during the first 3 to 7 days after exposure, after which they rapidly gained their weight to equal the weight of the controls. Guinea pigs surviving the lethal concentrations had a 25 percent loss in body weight during the first week after which the rate of gain equalled that of the controls, but their weights never returned to the control levels.

TABLE 2

LC50 VALUES FOR ANIMALS EXPOSED TO HF VAPOR

Species	Exposure Time	LC	50	19/20 Confidence Limits	Slope	Standard Error of the Slope
	min	mg/l	ppm	ppm	<u>-</u>	•
Rat	5	4.06	4970	4584 - 5388	11.8	<u>+</u> 4.2
Rat	15	5.50	2689	2397 - 3016	9.4	<u>+</u> 2.1
Guinea Pig	15	3.54	4327	4006 - 4672	15.5	<u>+</u> 4.8 •
Rat	30	1.67	2042	1901 - 2192	14.0	± 3•3
Rat	60	1.07	1307	1212 - 1410	10.7	± 3.8

2. Sub Lethal Exposures

Tables 3, 4 and 5 summarize the sub lethal exposures, at the various exposure times, showing species, concentrations, toxic signs, and pathologic changes.

a. 50 Percent of the LC50 Exposures

At these concentrations the toxic signs were about the same for both rats and rabbits. The toxic signs were respiratory distress lasting for a few hours after the exposure, eye and nasal discharge, pawing at the nose, and reddened conjunctive. Pawing at the nose continued for several hours after exposure. The animals appeared depressed and weak for at least 24 hours and appeared sluggish for an additional day. Nose and eye irritation usually were not seen after about 4 days.

b. 25 Percent of the LC50 Exposures

At this concentration level, rats and rabbits showed eye and nose irritation which were less severe than those seen in animals exposed at 50 percent of the LC50's. Pawing at the nose, reddened conjunctive, nasal and eye discharge, and sneezing were the usual toxic signs noted.

Dogs exposed to this concentration level showed eye blinking, periodic sneezing, coughing, and signs of general discomfort during the exposure. On withdrawal the dogs rubbed their nose and entire body on the grass for several hours after exposure, indicating some skin irritation. No visible skin lesions were noted. Although the cough seemed to disappear after a day or two, upon exercise it would reappear, finally ceasing after a week or 10 days. The hematologic studies showed no changes in the blood values.

c. 12.5 Percent of the LC50 Exposures

The effects of HF were similar to those seen at the 25 percent of the LC50 level but were less severe. The toxic signs seen in rats were: general discomfort, pawing at the nose, and tearing from the eyes. Most of these signs were mild and disappeared within a few hours after exposure. Dogs showed a mild eye irritation and sneezing on withdrawal and developed a dry non productive cough lasting about two days. They also rubbed their nose and body on the grass probably as a result of their skin irritation, but no lesions were noted. No changes in the hematologic values were noted.

d. 6 Percent of the LC50 Exposures

The effects seen in rats exposed to this concentration were milder as compared with those seen after exposure to higher concentrations. Occasional pawing at the nose and blinking of the eyes occurred, but no other toxic signs were observed. These signs disappeared shortly after withdrawal from the chamber.

TABLE 3

SUB LETHAL EFFECTS IN ANIMALS EXPOSED TO HE VAPOR FOR 5 MINUTES

Species	Concentr ppm 2432	mg/l	Toxic Signs Severe eye and masal irritation for at least 24 hours after exposed, weak and extremely uncomfortable.	Massive, darkened areas on lung surface up to 45 days after exposure.
	1438	1.18	Moderate eye and nose irritation - not as severe as at 50% of LC50.	Moderate, darkened areas on lung surface up to 45 days after exposure.
	749	0.61	Less severe eye and nose irritation.	Very few darkened areas on lung surface.

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TABLE 4

SUB LETHAL REPECTS IN ANIMALS EXPOSED TO HE VAPOR FOR 15 MINUTES

Species	Concentration ppm mg/1	ation mg/1	Toxic Signs	Pathology
Rats	1410	1.15	Severe eye and nose irritation lasting several days and sneezing. Weakness and extremely uncomfortable.	Darkened areas involving almost entire lungs up to 45 days after exposure.
	290	O.48	Some eye and nose irritation but not as severe as above. Sneezing.	Many darkened areas in lungs.
	376	0.31	Moderate eye and nose irritation.	Only few darkened areas on lungs.
	307	0.30	Mild eye and nose irritation.	No gross lesions seen.
Rabbits	1247	1.02	Severe eye and nose irritation lasting several days. Sneezing.	Darkened areas on lungs for first 14 days after exposure.
	458	69°0	Moderate eye and nose irritation.	Patchy darkened areas on lungs first 14 days after exposure.
Dogs	999	45.0	Eye and nose irritation, coughing, sneezing and mild skin irritation.	Very few small darkened areas on lungs.
	994	o.38	Mild eye and nose irritation, mild skin irritation. Coughing about 2 days after exposure.	Only an occasional small darkened area on lungs.

TABLE 5

SUB LETHAL EFFECTS IN ANIMALS EXPOSED TO HF VAPOR FOR 60 MINUTES

Species	Concer	Concentration	Toxic Signs	Pathology
	ndd	mg/1		
Rats	68 ₁₁	O4*0	Severe eye and nose irritation, sneezing, body weakness and generally discomfort.	Many darkened areas on lung up to $45~{ m days}$ after exposure.
Rats	291	0.24	Moderate eye and nose irritation and sneezing.	Many darkened areas on lungs but not as severe as above.
Rats	921	0.10	Mild eye and nose irritation and some sneezing.	Very few to no darkened areas on lungs.
Rats	103	90.0	Very mild eye and nose irritation.	No gross lesions noted.
Dogs	243	0.20	Sneezing, coughing and mild skin, eye, and nose irritation.	Few darkened patchy areas on lung.
Dogs	157	0.13	Rather mild eye, nose and skin irritation, sneezing and coughing to a mild degree.	No gross lesions seen.

B. Pathology

1. LC50 Exposures

The rats and guinea pigs surviving the LC50 exposures were sacrificed for gross pathologic examination at the end of the 14-day observation period. Some of the animals dying during or after the exposure were also examined. Darkened areas were seen on the surface of the lungs varying from a few patchy areas to large areas involving entire lobes. There seemed to be a relationship between the degree of lung damage and the mortality fraction. Enlarged darkened areas appeared to be more prevalent in the exposed groups than in the controls. All other organs examined grossly appeared similar to the controls.

2. Sub Lethal Exposures

a. 50 Percent of the LC50 Exposures

Gross pathologic changes were found in the lungs of rats and rabbits exposed to these concentrations regardless of exposure time. Dark areas of various sizes were seen in all exposed rats examined between 24 'nours and 45 days after exposure. In rabbits these dark areas were seen up to 14 days after exposure but not at 45 days. At 45 days after exposure it appeared that in both species the number of consolidated areas in the lungs were increased as compared with those in the controls.

b. 25 Percent of the LC50 Exposures

The gross pathologic changes found in the lungs of rats and rabbits at this exposure concentration were similar to those found at the 50 percent of the LC50 exposure, except that they were less severe. All other organs appeared similar to those of the controls.

Dogs had 4 to 5 dark, patchy areas on the surface of the lungs when sacrificed at 7 and 21 days after exposure. Other organs examined appeared similar to those of the controls.

c. 12.5 Percent of the LC50 Exposures

Only a few of the rats examined after exposure to this concentration had darkened areas on the lungs. These probably were not significantly different from those of the controls. Other organs examined were considered normal. No gross pathologic changes were seen in the dogs.

d. 6 Percent of the LC50 Exposures

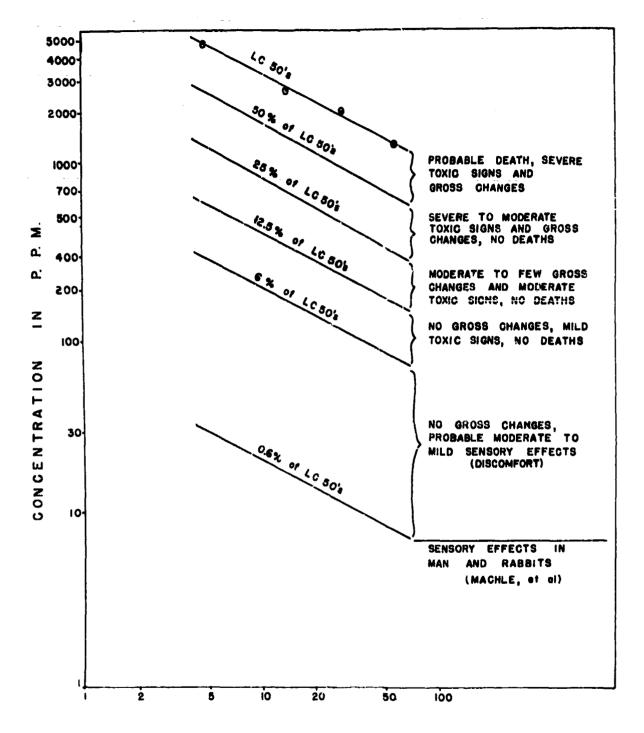
In rats no gross pathologic changes different from those in controls were noted in any of the organs examined.

DISCUSSION

As already mentioned, the criteria used in this study in evaluating the toxic effects of HF were the occurrence of toxic signs and the appearance of gross pathologic changes. In the early experiments concentration levels were used which produced positive gross effects in lungs. The concentration levels of HF were then progressively reduced by 50 percent until no gross pathologic effects were evident. At this level the sensory offects still were present, and the animals appeared uncomfortable. Figure 1 shows areas delineating toxic effects of HF to rats for varying exposure concentrations with varying times between 5 and 60 minutes. Since the actual LC50 values, established by experimentation, lie in a straight line when plotted against exposure time on loglog paper, it was assumed that the lines delineating the areas of the toxic effects would also be linear and parallel. At 6 percent of the LC50 concentrations, no gross pathology attributable to HF was found. However, it was observed that during exposure there was excessive eye blinking and pawing at the nose, suggesting discomfort. In the absence of microscopic tissue pathology, one would predict that below 6 percent of the LC50 concentration, no serious harmful effect would occur to animals exposed for short periods. The lower concentration limits at which essentially no sensory effects occur in man are not known. This lower limit shown in figure 1 was estimated from the work of Machle et al. who exposed rabbits as well as men for short periods to HF at a concentration of 0.025 mg/liter (0.6 percent of the rat LC50 for 5 minutes). There was evidence of irritation in the respiratory tract and a production of conjunctival and nasal discharge of the rabbits. Men expressed discomfort but could tolerate this concentration for several minutes. Mild smarting of the eyes and irritation of the large air passages occurred. No coughing or sneezing was seen.

The susceptibility of man to the effects of exposure to a low concentration of IIF is not known. Any estimates for safe concentration limits to man should be based on data from animals which are the most susceptible. Therefore an attempt was made to compare the susceptibility of the rat, rabbit, and dog to HF. Though the data are rather limited at various concentrations the 15-minute exposures give a rough comparison based on the toxic effects. From the descriptions of the toxic effects given in table 4, it appears that the rat is more susceptible than the dog. The rabbit's susceptibility is between the rat's and the dogs', but closer to the rats'.

When rats were exposed at 12.5 percent of the LC50, toxic signs were seen in all animals, but gross pathologic changes attributable to the exposure were present in only a few of these. In order to show complete absence of pathology it was necessary to examine another group of rats which were exposed to a lower concentration, namely 6 percent of the LC50. In this group the changes associated with HF effects were absent. The toxic signs were mild eye and nose irritation. These signs were primarily sensory responses. If it can be assumed that there is a similarity between our exposures and those reported by Jilverman et al. (4), then we must consider



TIME IN MINUTES
Figure 1

AREAS DELINEATING TOATC SPRECTS OF HE TO MATS AT WARIOUS EAPOURS CONCENTATIONS FOR 5 TO 60 MINUTES

an additional factor for man, namely the comfort level of HF. Silverman stated that for some industrial solvents the sensory limits for man were lower than the suggested MAC's. It may well be that for short exposures this is also true for HF. Since Machle et al. have shown that man does not become insensitive to this vapor, the sensory effects retain their usefulness after repeated exposures. On the other hand, if estimates for safe concentration limits for man are to be based on toxic signs and pathologic changes in animals, it is believed that 6 percent of the LC50 for the rat is a reasonable level from which these estimates may be made.

SUMMARY

Rats, dogs, rabbits, and guinea pigs were exposed to various concentrations of HF for 5- to 60-minute periods. The toxic signs observed in the animals and the changes in gross pathology of the lungs correlated directly with the severity of the exposure. At a given concentration rabbits and dogs were less affected than rats. The concentrations of HF causing mild toxic signs and no gross lung changes in rats were 307 ppm (0.3 mg/liter) and 103 ppm (0.08 mg/liter) for 15 and 60 minutes, respectively.

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+	ASD TR 61-744	U.S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland THE RESPONSE OF ANMALS INHALING HYDROGEN FLUORIDE FOR SINGLE, SHORT EXPOSURES, by T. R. Carson, et al. December 1961. 20p. incl. illus., tables. 6 refs. (Proj. 7165; Task 716501) Rats were exposed to various concentrations of HF for single 5-, 15-, 30-, and 60-minute periods, and the LC50's were calculated. Guinea pigs were exposed for 15 minutes to various concentrations and the LC50's were calculated. Guinea pigs were exposed for 15 minutes to various concentrations and the LC50 calculated. In addition to the lethal exposures, rats, dogs, and rabbits were exposed to	ASD TR 61-744	lower concentration levels ranging from 6 to 50 percent of the rat LC50's. The toxic signs were eye and masal irritation. There were gross changes in the lungs of all species exposed to HF at the higher concentrations. The signs and pathologic changes decreased in severity as the concentration levels were lowered. At a given concentration mild toxic signs and rabbits tolerated HF better than rats. The concentrations of HF causing mild toxic signs and no gross changes in the lungs of rats were 307 ppm (0.3 mg/liter) and 103 ppm (0.08 mg liter) for 15 and 60 minutes, respectively.	
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